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MYOCARDIAL FUNCTION IN ENDOTOXIN SHOCK.(U)

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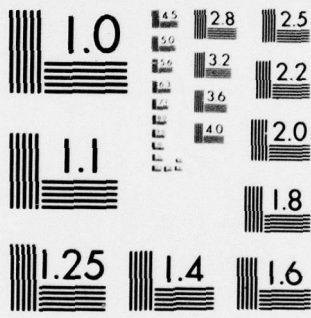
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TECHNICAL REPORT NO. 132

MYOCARDIAL FUNCTION IN ENDOTOXIN SHOCK

Lerner B. Hinchaw

Prepared for Publication

in

Circulatory Shock

University of Oklahoma Health Sciences Center
Department of Physiology & Biophysics
Oklahoma City, Oklahoma

28 August 1976

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The insidious and sometimes precipitous development of septic shock in man involves mechanisms not clearly understood. Although the comparable animal model, utilizing endotoxin or live E. coli, has been studied extensively in recent years, the precise mechanisms involved in the development and maintenance of the shock state are also unclear. Recent emphasis has been focused on the causes of inadequate tissue perfusion in this form of shock.

Of particular importance to this presentation are the causes of diminished cardiac output observed in lethal human septic shock (1) and in the canine species administered endotoxin (2-5). Several explanations have been proposed to account for the decrease in cardiac output, and the purpose of this paper is to consider the role of myocardial function in the canine model subjected to endotoxin shock. Results will be discussed concerning experiments conducted in this laboratory on intact dogs and isolated working heart preparations subjected to LD₆₀-LD₁₀₀ E. coli endotoxin.

Role of venous return in endotoxin shock

Initial studies carried out in canine endotoxin shock suggested that cardiac function is unimpaired during the early phase of shock and that the predominant effect on cardiac output is an initial decrease in venous return due to peripheral pooling (2). Our laboratory has documented notable decreases in venous return during the first hour after endotoxin in both the canine and nonhuman primate species (3-5). The technique used in monitoring changes in venous return developed by Weil et al. (2) was utilized in our experiments in dogs and monkeys and is shown in Figure 1A. Total venous return is passively drained from the cannulated inferior and superior vena caval vessels into a

reservoir and returned at constant flow via a pump to the cannulated right atrium (2-4). Decreases in the volume of blood in the reservoir indicate decreases in venous return due to peripheral pooling, since cardiac inflow is maintained constant and left and right atrial pressures are relatively unchanged. This useful procedure distinguished between primary myocardial dysfunction and decreased venous return, and the latter clearly accounted for the drop in cardiac output during the early phase of endotoxin shock (3,4). These findings strongly suggest that peripheral pooling mechanisms predominate in the early period of endotoxin shock, and there is no evidence for an early detrimental effect of endotoxin on the myocardium either as a direct toxic action or as a result of unfavorable circulatory changes.

Myocardial function in endotoxin shock

Although earlier observations failed to document the development of myocardial dysfunction during the first hour of endotoxin shock (2-4), several reports provided evidence that the heart is depressed during later phases of shock in animals given endotoxin (6-8), while clinical studies also documented cardiac dysfunction in human septic shock (9,10). Since the publication of these reports (6-10), we have conducted experiments to determine the effects of endotoxin shock on the myocardium. We have utilized an isolated working heart preparation exchanging blood with an intact anesthetized support dog (11-19), diagrammatically described in Figure 1B. Blood from the support dog is delivered at a constant rate to the pulmonary artery of an isolated heart obtained from a donor animal and both aortic outflow and coronary venous return are periodically measured, sampled and returned to the animal via the femoral vein. Mean aortic pressure of the isolated heart is main-

tained constant except during tests of myocardial performance when it is altered through a wide range of pressures by means of an adjustable screw clamp on the aortic outflow tubing (Figure 1B). Since both cardiac inflow and mean aortic pressure are controlled, changes in left ventricular end diastolic pressure (LVEDP), positive and negative dP/dt_{\max} , cardiac power and myocardial efficiency are readily compared to control, pre-endotoxin values (15,18,19) and myocardial function can be readily assayed. In our experiments we injected endotoxin to each or both animals (heart donor and support animal) prior to transferring the heart to the isolated state of perfusion, and in separate studies we also administered endotoxin to both isolated heart and intact support dog following transfer of the heart.

Table 1 summarizes our findings in venous return preparations, intact animals and isolated heart experiments. The time in hours after endotoxin administration for evaluation of heart function is noted in the left column, while the results, with references cited, are listed in the right column. Each time period studied therefore corresponds to a separate paper published by this laboratory (3,4,11,13-16,19-24). Criteria for the adverse effect of endotoxin on myocardial function are increases in LVEDP, decreases in $+dP/dt_{\max}$ and $-dP/dt_{\max}$, and depressions in cardiac power and efficiency. From examination of Table 1, several observations emerge: (a) During the early phase of shock (1-3 hours) there is no evidence for cardiac dysfunction; cardiac output falls because of a decrease in venous return due to pooling of blood in the periphery. (b) Blood from dogs 6-18 hours in endotoxin shock does not contain a myocardial depressant factor of sufficient potency to depress the function of a normal heart following exchange of blood between the intact shocked animal and the isolated heart from a non-shocked dog.

(c) The minimum prerequisite for the development of myocardial dysfunction is that the assay donor heart must be present at the time of endotoxin injection, either before or after its transfer to the isolated state, and the minimal time for failure after endotoxin is 3 hours. (d) Severe mitochondrial edema and disruption occur within 7-9 hours after endotoxin, suggesting the onset of irreversibility of the state of shock.

Mechanisms of myocardial dysfunction in endotoxin shock

(a) Coronary hypoperfusion. Results from our studies have clearly implicated the importance of coronary perfusion in endotoxin shock (19,25). We have explored the separate roles of coronary hypotension and endotoxin in the pathogenesis of heart failure. Experiments were performed on isolated canine hearts supported by blood from intact dogs (19). The first series of hearts was subjected to 4 hours of coronary hypotension plus endotoxin, while the second series was subjected to low coronary pressure alone. Ninety percent of hearts subjected to both endotoxin and decreased pressure demonstrated dysfunction at 4 hours post-endotoxin, as evidenced by increased LVEDP, decreased negative dp/dt_{max} and depressed efficiency. In contrast, 40% of the hearts subjected to low pressure alone demonstrated dysfunction at 4 hours (19). These findings suggest that inadequate coronary blood flow performs a significant role in the precipitation of heart dysfunction in endotoxin shock.

Experiments also demonstrating an important role of coronary perfusion after endotoxin were reported in the retrograde-perfused canine heart with supported coronary circulation (25). Maintained perfusion of the coronary

circulation by pump perfusion improved heart function during 5 hours of endotoxin exposure: improved length-tension relationships were observed (25). In support of these studies we observed marked cardiac dysfunction in dogs following LD₁₀₀ injections of endotoxin in which severe systemic hypotension occurred and early deaths were recorded (15,16). In similar experiments eliciting marked systemic hypotension, extensive cardiac mitochondrial edema and disruption were observed at times of heart failure, between 5-7 hours post-endotoxin injection (20). Experiments strongly suggesting the protective effect of increased coronary flow after endotoxin on the myocardium were those conducted by our laboratory utilizing methylprednisolone sodium succinate (24), sodium nitroprusside (26) and insulin (27,28). In these experiments increased coronary blood flow was commonly associated with improved myocardial performance, including decreased LVEDP and increased positive and negative dP/dt_{max} .

(b) Depressed responsiveness to inotropic stimuli. An early observation in our laboratory was that when the heart was removed from an endotoxin-shocked animal and perfused with blood from a support dog, it appeared flaccid and contracted weakly. Studies were subsequently designed to study this phenomenon: hearts were transferred to the isolated perfused state 2 hours following LD₇₀ endotoxin administration to the intact heart donor animal. Findings showed decreased responsiveness of the left ventricle to epinephrine infusions into the left atrium, on the basis of depressed changes in positive and negative dP/dt_{max} , cardiac power, efficiency and coronary blood flow, in contrast to experiments in which endotoxin was not administered (22). It was also noted in earlier heart studies that within 5-6 hours post-endotoxin, the heart could not perform at elevated afterloads unless

driven by inotropic agents (15). It was concluded from these experiments that myocardial contractile and relaxation characteristics and coronary vascular responses to catecholamines are depressed in endotoxin shock during the period of depressed myocardial function.

(c) Intracardiac ionic and fluid disturbances. Our previous reports suggested that various intracardiac disturbances of unknown origins are partly responsible for the precipitation of myocardial dysfunction after endotoxin. It is probable that there is a close association between the appearance of heart edema, the decrease in negative dP/dt_{\max} and abnormal concentrations of K^+ , and perhaps also Ca^{++} , manifested at the time when cardiac dysfunction is first revealed. Ionic imbalances may have resulted from increases in coronary capillary and myocardial cell membrane permeabilities, exacerbated by the accumulation of edema fluid between and within contractile elements and in the mitochondria (16,20,23,24,27,28). The mechanism of the development of heart edema after endotoxin is unknown although it appears to be an early critical stimulus for the onset of myocardial dysfunction (23). Pre- and post-coronary capillary vascular resistance changes may be responsible for the development of edema after endotoxin. If so, the marked improvement of performance after nitroprusside observed in this laboratory may have been elicited on the basis that coronary vasodilatation would decrease fluid extravasation by reducing the ratio of pre- to post-capillary resistance; i.e., by notably decreasing coronary venous resistance (26). Abnormalities in intracardiac ion concentrations might be enhanced by increased coronary capillary permeability. Digoxin was found to be remarkably effective in preventing and reversing cardiac dysfunction in endotoxin-shocked animals (16).

Both the severe mitochondrial edema and disruption of mitochondria were prevented by early digoxin treatment (20), and its chief action may have been to enhance myoplasmic concentrations of calcium lost via cell membrane leakage, thus resulting in more forceful contractions (16). We also found intracardiac infusions of insulin remarkably effective in restoring heart function to normal after endotoxin (27,28). A consistent fall in arterial blood concentrations of potassium occurred following infusion of insulin in these experiments, suggesting the restoration of cell membrane potential leading to improvement of the myocardial contractile state. Negative dp/dt_{max} increased after insulin (27,28), which may have occurred following restoration of normal fluid balance with the return of ionic distributions to normal, including potassium (28) and ATP-dependent calcium uptake by the sarcoplasmic reticulum (22).

(d) Blood-borne myocardial depressant substances. Searching for evidence of a circulating factor in shock capable of depressing myocardial function (MDF) has been a continuing goal of this laboratory. However, our attempts to implicate MDF in both endotoxin shock and splanchnic arterial occlusion (SAO) shock have thus far been fruitless (11,12,14,17,18,21).

Our early experiments demonstrated that animals subjected to 3 hours of endotoxin shock and a concomitant period of severe systemic hypotension showed no evidence of myocardial dysfunction (11). We concluded that a myocardial depressant factor of sufficient potency to elicit heart dysfunction was not present under the conditions of these experiments. However, it was thought possible that an MDF effect may have been masked by the simultaneous elaboration of catecholamines. Studies were therefore carried out utilizing beta adrenergic blockade (propranolol) (12). When endotoxin was administered

to an isolated working heart during beta adrenergic blockade, there was no evidence of myocardial dysfunction for a 2-hour period (12). Results from these experiments strongly supported the position that MDF was not present during the 2-hour period of endotoxin shock.

We next considered the possibility that insufficient time elapsed during the shock state for a sufficient concentration of MDF to accumulate in the blood. Experiments were therefore conducted with times in shock ranging from 6 to 21 hours (14,21). Endotoxin was administered to intact dogs, and hearts from non-shocked animals were placed into perfusion systems with these animals at various times post-endotoxin. In no instance was there any evidence of myocardial dysfunction of the assay heart, even if the endotoxin-treated animals were in the preterminal stage of shock (14,21). Stroke work, cardiac power, LVEDP, dP/dt_{max} , isometric tension, myocardial efficiency and force velocity curves were all within the normal range during the 6-21 hour time span. Results from these experiments strongly suggested the absence of a myocardial depressant substance in the blood at any time following administration of endotoxin.

Since MDF is reported to be released primarily from the pancreas (29,30) under the conditions of shock, we considered the possibility that the splanchnic circulation in our experiments might not have been sufficiently insulted to elicit the release of MDF. To explore this possibility, we conducted experiments on dogs in splanchnic arterial occlusion (SAO) shock. Two hours of total ischemia were produced by occluding the celiac, superior and inferior mesenteric arteries. Following release of the occlusions, we observed the effects of blood leaving the previously occluded splanchnic region on an isolated working heart exchanging blood with the shocked animal in a system

as shown in Figure 1B. In no instance was there any evidence of myocardial dysfunction of the assay heart for 1-2 hours or until death of the animal following a period of profound systemic hypotension (18). These experiments should have elicited a maximal MDF effect because of the profound insult both to the splanchnic circulation and the pancreas (29,30). Findings from these studies strongly suggested the absence of a myocardial depressant factor in shock even under the most favorable conditions for its release.

After careful consideration of these findings, we decided to conduct a more crucial test to determine if MDF is elaborated in shock: In separate experiments (17), the isolated assay heart was placed on the brink of failure prior to release of the splanchnic arterial occlusion by subjecting the heart to a 2-4 hour period of hypoperfusion at coronary artery pressures between 30-50 mmHg (17). However, even in these experiments following release of the splanchnic arterial occlusions of 2 hours' duration, there was no evidence of myocardial dysfunction of the slightest degree for 1-2 hours or until death of the shocked animal.

We concluded from the foregoing experiments (17,18) that either MDF is totally absent in shock, or if present, it is innocuous to the myocardium, and is therefore not a factor in accounting for myocardial dysfunction in SAO and endotoxin shock.

Our experiments to this point had failed to demonstrate cardiac dysfunction in endotoxin shock or splanchnic arterial occlusion shock and had also failed to implicate a myocardial depressant factor in these two forms of shock. We decided to turn our attention to a new approach, looking for a different set of factors which might better explain the role of the heart in shock. It was decided to administer endotoxin to the dog supplying the heart rather than to

the support dog ultimately supplying blood to the isolated heart. The results were dramatically different from the previous studies: Donor hearts either receiving endotoxin prior to transfer to the isolated state, or following transfer, demonstrated severe myocardial dysfunction within 4-9 hours following endotoxin administration (15,16,23,24). These findings clearly demonstrated that the heart to be tested for function (the donor heart) must be present at the time endotoxin is administered in order to exhibit dysfunction at any time after endotoxin. In contrast, as shown above, in no instance will a normal heart receiving blood from an endotoxin-shocked animal demonstrate dysfunction, regardless of the degree of severity or time in shock.

Finally, we planned an experiment to evaluate the possible role of a myocardial depressant factor released from the pancreas. Heart donor animals were acutely depancreatized and given endotoxin, and 4-6 hours later myocardial function was evaluated in the isolated state as in the previous studies (15,16, 23,24), while the heart was exchanging blood with an intact support animal (18). All of these hearts demonstrated typical failure just as those in the previous experiments (15,16,23,24). The absence of the pancreas in the heart donor animals did not preclude the development of myocardial dysfunction after endotoxin, while hearts from depancreatized control dogs not receiving endotoxin showed completely normal functional characteristics in the isolated working state (18).

In summary, these findings taken together demonstrate that a myocardial depressant factor does not perform a significant role in endotoxin shock or splanchnic arterial occlusion shock. The basis for this conclusion is that (a) blood from dogs 6-21 hours in all stages of endotoxin shock does not depress myocardial function; (b) beta adrenergic blockade fails to unmask

an MDF effect; (c) blood from dogs in lethal splanchnic arterial occlusion (SAO) shock does not depress myocardial function of a normal heart or one placed on the brink of failure by coronary hypoperfusion; and (d) acute pancreatectomy does not prevent myocardial dysfunction after endotoxin; however, pancreatectomy without endotoxin does not result in depressed cardiac function during the course of the experiments.

Summary of suggested adverse effects of endotoxin on the myocardium

Figure 2 summarizes our current understanding regarding the causes of myocardial dysfunction in endotoxin shock. Coronary hypoperfusion and depressed responses to beta adrenergic stimuli are prime factors in the elicitation of cardiac dysfunction. Intracardiac disturbances perform a major role but their causes are obscure. Associated together in this latter category are the development of edema in the myocardium occurring in both the contractile elements and mitochondria; ionic imbalances of potassium and probably calcium; and elevations of left ventricular end diastolic pressure and depressions of negative dP/dt_{\max} , cardiac power and efficiency. The interactions and additive effects of these factors are responsible for the development of myocardial dysfunction in endotoxin shock.

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TABLE 1. MYOCARDIAL FUNCTION IN ENDOTOXIN SHOCK

| Time post-endotoxin (hours) | Endotoxin administration | Myocardial effects of endotoxin and references cited |
|-----------------------------------|---|---|
| <u>WHOLE ANIMAL EXPERIMENTS</u> | | |
| 1 | "Venous return" experiment | No adverse cardiac effect, but a decrease in venous return occurs (3,4) |
| 7-9 | Intact animal | Severe myocardial mitochondrial edema and disruption (20) |
| <u>ISOLATED HEART EXPERIMENTS</u> | | |
| 1-3;6; 18-21 | Endotoxin to support dog only | No adverse myocardial effect* (13,14,21) |
| 1-3 | Endotoxin to both heart and support dog | No adverse myocardial effect* (11) |
| 3-4;4 | Endotoxin to both heart and support dog | Myocardial dysfunction* (19,22) |
| 4-7;4-8; 5-7;6-9 | Endotoxin to heart dog only | Myocardial dysfunction* (15,16,23,24) |

*Criteria for adverse effect of endotoxin on function: Increase in LVEDP; decreases in $+dP/dt_{max}$, negative dP/dt_{max} , cardiac power and efficiency

FIGURE 1. DIAGRAMMATIC PRESENTATIONS OF METHODS USED TO DISCRIMINATE BETWEEN VENOUS RETURN AND CARDIAC OUTPUT DURING ENDOTOXIN SHOCK (ARROWS DESIGNATE DIRECTION OF BLOOD FLOW)

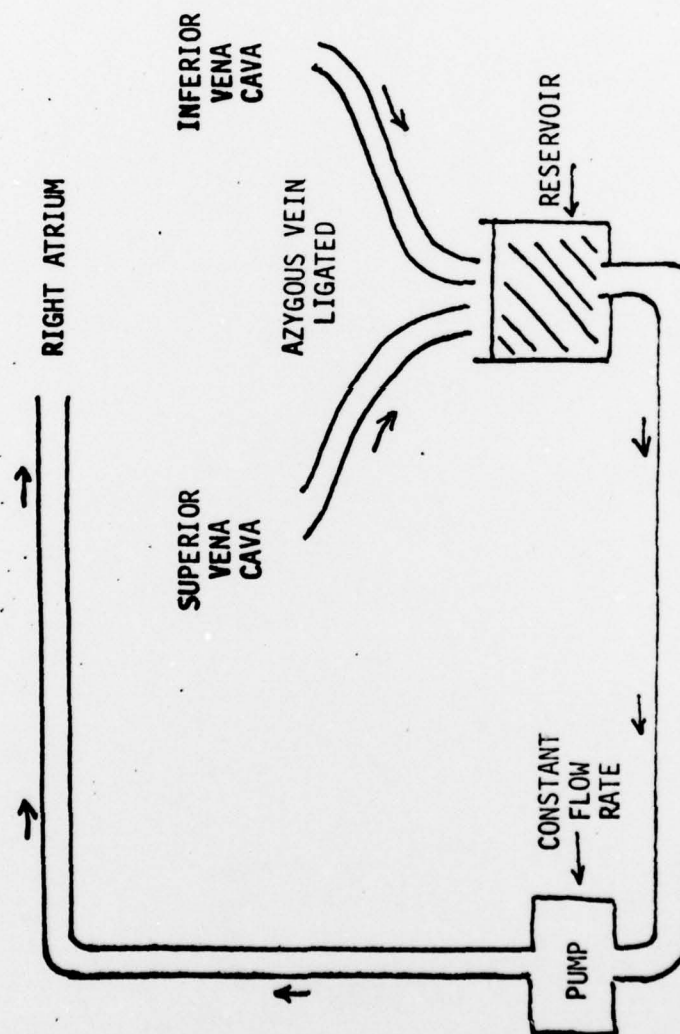


FIGURE 1A. VENOUS RETURN PREPARATION.

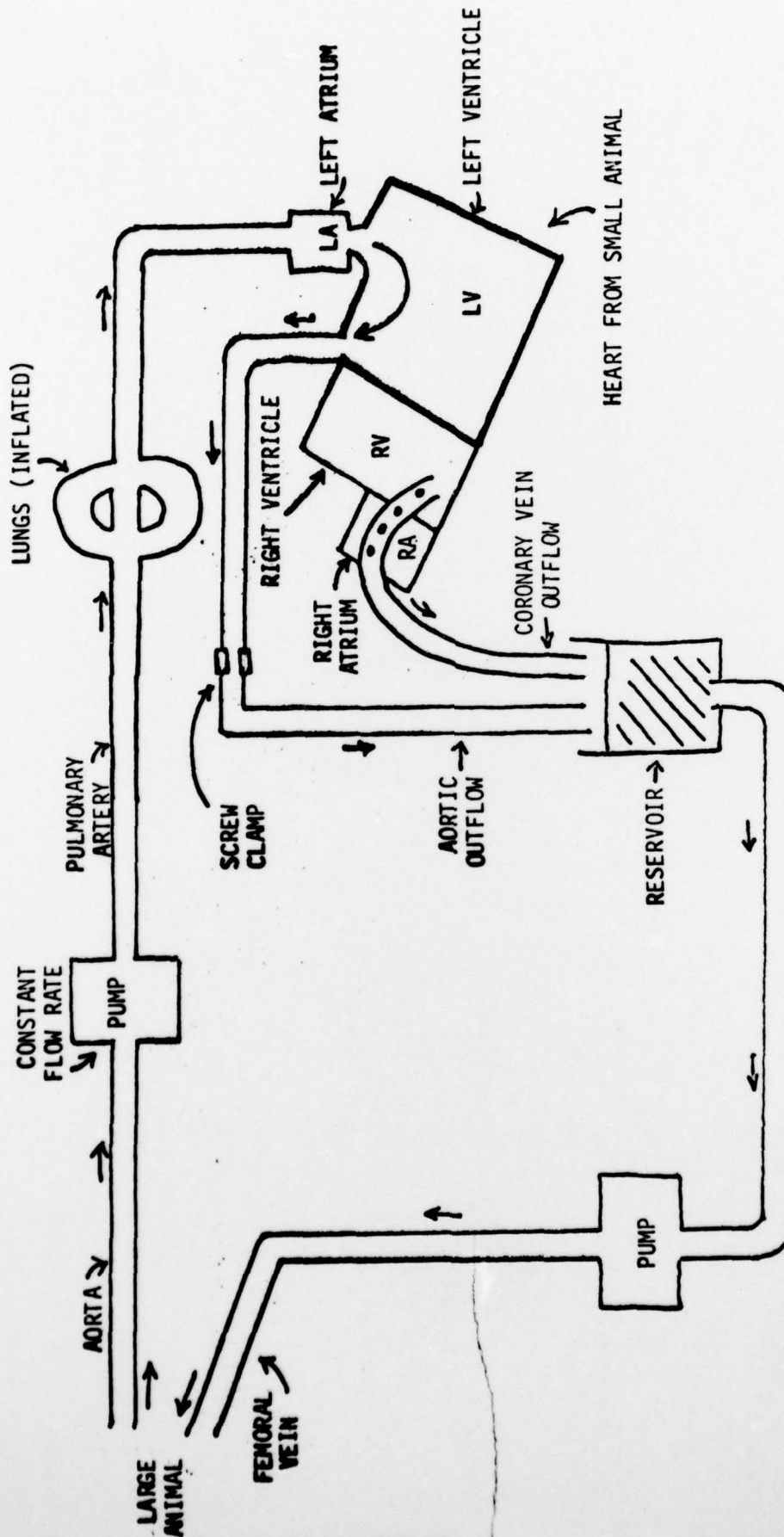


FIGURE 1B. ISOLATED WORKING HEART PREPARATION

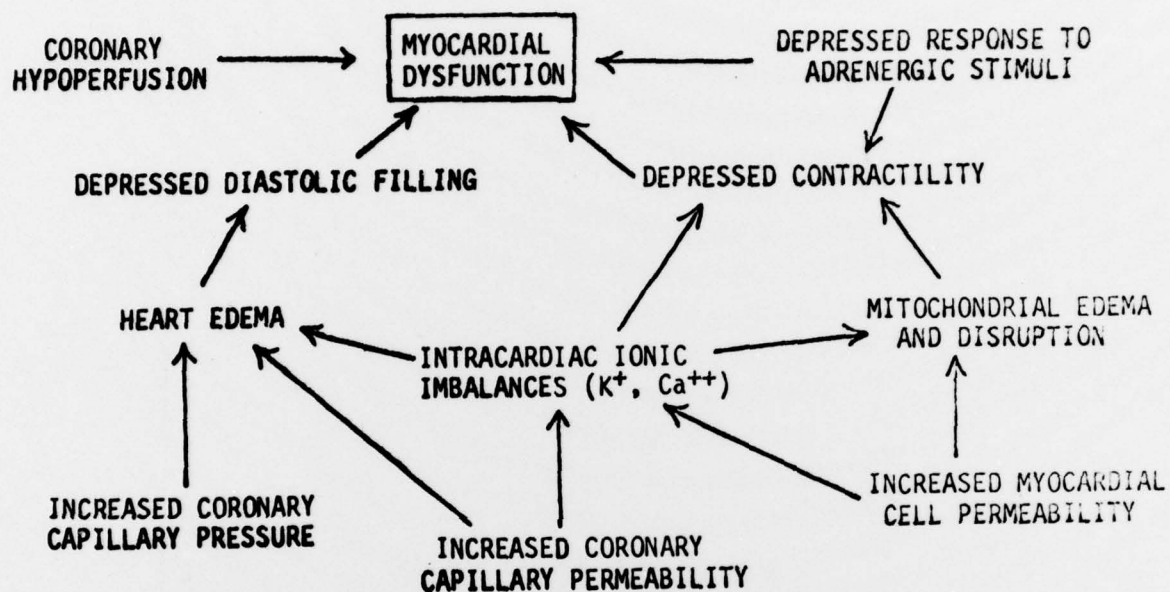


FIGURE 2. SUGGESTED ADVERSE EFFECTS OF ENDOTOXIN ON THE MYOCARDIUM

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| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number) ★ Coronary hypoperfusion and depressed responses to beta adrenergic stimuli are prime factors in the elicitation of cardiac dysfunction. Intracardiac disturbances perform a major role but their causes are obscure. Associated together in this latter category are the development of edema in the myocardium occurring in both the contractile elements and mitochondria; ionic imbalances of potassium and probably calcium; and elevations of left ventricular end diastolic pressure and depressions of negative | | |

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dP/dt_{max} , cardiac power and efficiency. The interactions and additive effects of these factors are responsible for the development of myocardial dysfunction in endotoxin shock.

$dP/dt_{sub max}$

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- (1) Department of the Army
U. S. Army Science and
Technology Center - Far East
APO San Francisco 96328
- (1) Assistant Chief for Technology
Office of Naval Research, Code 200
800 N. Quincy Street
Arlington, Virginia 22217